Changes in pain and quality of life in depressed individuals with spinal cord injury: does type of pain matter?

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Objective: To examine the association of neuropathic and nociceptive pain severity and interference with quality of life (QoL) in persons with spinal cord injury (SCI) who underwent a randomized controlled 12-week trial of an antidepressant to treat depression. A secondary objective was to assess the effect of changes in pain on mobility and physical independence.
Design: Multivariable ANCOVA models controlling for relevant demographic covariates, treatment condition, and baseline pain and QoL were used.
Setting: Six rehabilitation centers.
Participants: Of the 133 persons who were randomized into the trial, 108 provided pain severity and interference ratings through follow-up.
Interventions: Not applicable.
Outcome Measures: The Satisfaction with Life Scale and the physical and mental component summary scores of the 12-Item Short-Form Health Survey (SF-12). Secondary outcome measures included the mobility and physical independence subscales of the Craig Handicap Assessment and Reporting Technique (CHART).
Results: Broadly, few associations between pain and QoL were evident. Results revealed relationships between lower baseline nociceptive pain interference and higher satisfaction with life and mental health-related QoL at 12 weeks. Similarly, lower neuropathic pain interference was associated with change in physical independence, but unrelated to mobility.
Conclusions: Pain interference over time may be differentially related to QoL outcomes based on the type of pain following SCI, but overall, there were no extensive relationships between pain and QoL in this sample of depressed persons with SCI.

Keywords: Spinal cord injury, Pain, Neuropathic pain, Quality of life

Introduction

Approximately 70% of persons with spinal cord injury (SCI) experience chronic pain,[1] with the majority reporting multiple pain types.[2] Pain has pervasive negative effects on mood and psychosocial functioning,[3,4] occupational activities,[5] sexuality[6] and basic needs such as sleep.[7,8] Therefore, it is not surprising that pain after SCI, is consistently associated with lower quality of life (QoL) post injury.[9–11]

Although the relationship between SCI-related pain and QoL has been well documented,[12–17] most studies have been cross-sectional, limiting understanding of changes over time. Based on the longitudinal data that exist, pain remains a strong predictor of QoL. Within the first year following injury, persons with SCI-related pain were more likely to experience deterioration in satisfaction with life,[18] and less pain during the acute phases of injury was associated with a recovery of life

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satisfaction at 1 year follow-up.[19] Between the first and second year following SCI, increased pain interference was associated with a decrease in life satisfaction.[20] In one of the most extensive studies to date on the matter, only pain severity and functional limitations were significant predictors of persistently low life satisfaction from rehabilitation to 5 years post SCI.[21]

An important gap in the literature is that prior studies have not accounted for the influence of pain type on QoL following SCI. Most pain taxonomies broadly classify SCI-related pain into two types: nociceptive (musculoskeletal, visceral, other) and neuropathic, and indicate where, relative to the location of the injury, the particular type of pain is experienced.[9,22] Types of SCI-related pain are distinguished by the different purported mechanisms by which they develop and persist, which is reflected in the quality of pain and pain symptom profile that is experienced. Not accounting for the various pain types in SCI research may confound the effects of pain under study,[23,24] and in this case, the relationship between pain and QoL following SCI.

The current paper examines the relationship between pain, pain interference, and QoL within a community-based sample of persons with SCI who participated in a placebo-controlled antidepressant trial to treat depression.[25] In that trial, a reduction in depression severity was associated with improved QoL[26] and in a separate analysis, treatment with venlafaxine XR improved nociceptive pain, but not neuropathic pain.[27] However, the relationship between pain and QoL was not examined. We hypothesized that a reduction in pain would be associated with improved QoL over the course of the trial when accounting for treatment condition. Moreover, increased QoL would be most correlated with changes in non-neuropathic/nociceptive pain, since this type of pain is often affected by movement[22] and improved mobility is associated with improved QoL among those with SCI.[10] To this end, the relationship between both types of pain and mobility and physical independence at follow-up were also examined.

Methods

Data came from a multicenter, double blind placebo controlled trial entitled *the Project to Improve Symptoms and Mood after SCI (PRISMS)*. The purpose of the PRISMS study was to examine the efficacy of venlafaxine XR for the treatment of depression in SCI. The methodology and primary results can be found elsewhere.[25,28] The study was approved by each of the respective site's internal review board.

Participants

In the parent trial,[25] a total of 2536 subjects with traumatic SCI were screened and 133 were eligible for and consented to the trial. Sixty-four individuals were randomized to receive placebo and 69 individuals were randomized to the venlafaxine condition. Of the 133 enrolled, 122 reported pain and 108 provided pain severity and interference ratings from baseline through the 12-week follow-up. To be included in the study, participants had to be between 18–64 years old, have traumatic SCI of at least one-month duration, meet diagnostic criteria for major depressive disorder or dysthymic disorder, and obtain score of 10 or more on the Patient Health Questionnaire-9.[29] Participants were excluded if they were non-English speaking, had cognitive impairment to the degree that would invalidate self-report measures, had severe psychiatric condition, current drug or alcohol dependence; were scheduled to have surgery or a major medical procedure within three months, were hospitalized, had an unstable medical condition or were pregnant.

Measures

Quality of life was assessed via two measures: the 12-item Medical Outcomes Study Short Form Survey (SF-12)[30] and the Satisfaction with Life Scale (SWLS).[31] These measures were administered at baseline and at the end of the 12 week trial. The SF-12 is a shorter alternative (12 items) to the Medical Outcomes Study Short-Form 36 Health Survey (SF-36)[32] and similarly provides a Physical Component Summary (PCS) and Mental Component Summary (MCS) score. The SF-12 is a generic health-related quality of life measure used in SCI research previously,[33–35] and has been shown to have a high correlation with the SF-36.[34,36] The SWLS[31] is a measure of an individual's subjective global judgment of their life. It is a five-item scale, with responses on each item ranging from 1 (low satisfaction) to 7 (high satisfaction). The total score is the sum of the item scores and can range from 5 to 35. Diener[37] has provided ranges in which to further interpret SWLS scores as follows: 0–5 (extremely dissatisfied), 10–14 (dissatisfied), 15–19 (slightly below average in life satisfaction), 20–24 (average life satisfaction), 25–29 (high life satisfaction), and 30–35 (very high life satisfaction/highly satisfied). The SWLS has previously demonstrated good psychometric properties in a population with SCI.[38]

The Craig Handicap Assessment and Reporting Technique (CHART)[39] is a 32-item measure of disability across 6 domains that has demonstrated good psychometric properties across varying levels of

impairment.[40] The CHART was administered at baseline and again at the 12-week follow-up. For the current analyses, changes in Mobility and Physical Independence subscale scores were used.

Pain classification

As has been suggested previously,[23,24] participants were asked to report up to three distinct pain sites on their body at baseline, and these same pain sites were assessed in terms of severity and pain interference at 6- and 12-week follow-up. Pain sites were classified as neuropathic or nociceptive (non-neuropathic) using the Spinal Cord Injury Pain Instrument (SCIPI).[41] The SCIPI is comprised of 4 items that assess qualities suggestive of neuropathic pain: (1) electric/shock like, (2) pins and needles, (3) skin feels hot/cold, and (4) in an insensate area. An endorsement of two or more items defined neuropathic pain; anything less was considered non-neuropathic pain. The SCIPI has been shown to have good accuracy and validity when compared to independent clinician ratings, with a sensitivity and specificity of 0.72 and 0.78, respectively.[41]

Pain severity and interference

Pain severity was measured using a 0 (no pain) to 10 (worst pain imaginable) numeric rating scale (NRS). Participants were asked to rate, for each pain site, the average pain severity experienced over the past week. To measure the degree to which pain from each site interfered with activities, the interference items from the Brief Pain Inventory[42] were used. These are seven items, which ask the participant to rate, on a scale of 0 (no interference) to 10 (completely interferes), how much their pain interfered with daily activities. Pain severity and interference ratings obtained at baseline and at 12 weeks were used in the analyses of the current study.

Demographics and clinical covariates

Demographic and psychosocial factors that may affect QoL were also accounted for in the analyses. These included pertinent demographics and injury characteristics, whether the individual received the study treatment (venlafaxine XR vs. placebo), and levels of depression and anxiety. Race/ethnicity was the only categorical variable that was dichotomized (White, non-Hispanic versus non-White) for regression analyses. Severity of depressive symptoms was measured via the Patient Health Questionnaire-9 (PHQ-9).[29] The PHQ-9 is a brief screen for depression that has demonstrated good psychometric properties among rehabilitation populations including SCI.[43] The Generalized Anxiety Disorder-7 (GAD-7),[44] a brief measure with demonstrated reliability and validity, was used to measure anxiety.

Statistical procedures

Pain was quantified in the regression modeling by calculating the average pain for all sites. If a subject reported fewer than three pain sites at baseline, we imputed zeroes for the remaining sites before calculating their overall three-site average, and adjusted for the number of actual pain sites in the regression. Overall scores were calculated for both the intensity and interference ratings. Separate scores were also calculated for neuropathic and nociceptive pain.

Differences in demographic and injury characteristics (Table 1) between individuals with and without pain were assessed statistically using Mann-Whitney and Fisher Exact tests as appropriate. A sensitivity analysis revealed no significant differences between those providing pain data through follow-up and the baseline sample. QOL outcomes were modelled using standard linear regression. Separate models were constructed for neuropathic and nociceptive pain, each of which included only those subjects who had the relevant type of pain. Individuals with multiple pain sites reflecting both types of pain therefore contributed data to each model. For each regression model, an ANCOVA approach was used such that the QOL score obtained at the 12-week follow-up was regressed on the baseline and 12-week follow up pain score. Models were adjusted for site given data were from a multisite trial. Baseline QOL was controlled for and additional effects were included for treatment arm (venlafaxine or placebo) and the number of pain sites (1–3). Additionally, a forward selection procedure on the demographic and injury characteristics listed in Table 1 was used to help determine which of these variables were also to be included in all of the models.

Results

Participants were mostly men, were of white, non-Hispanic ethnicity , never married, and unemployed. Of the participants reporting NP pain, most were between the ages of 30–44 and also 45–59. The highest proportion of participants reporting any NC pain also fell into these two age categories. The majority of participants included in both NP and NC pain samples had complete SCI (AIS grade A) at the thoracic level or below (paraplegia) and had been injured, on average, for approximately 11 years. The most common cause of SCI was motor vehicle collision followed closely by gunshot wound. For full descriptive

Table 1 Demographic and injury characteristics of participants with and without neuropathic pain and nociceptive pain

	Any NP Pain			Any NC Pain		
Variable	No N = 42	Yes N = 79	P	No N = 45	Yes N = 77	P
Site	3 (7%)	6 (8%)	0.586	2 (4%)	8 (10%)	0.257
UW	11 (26%)	17 (22%)		14 (31%)	14 (18%)	
UAB	4 (10%)	15 (19%)		5 (11%)	14 (18%)	
UM	13 (31%)	28 (35%)		18 (40%)	23 (30%)	
RIC	8 (19%)	11 (14%)		5 (11%)	14 (18%)	
BIR	3 (7%)	2 (3%)		1 (2%)	4 (5%)	
Miami	3 (7%)	6 (8%)		2 (4%)	8 (10%)	
Treatment Arm						
Placebo	22 (52%)	41 (52%)	1.000	24 (51%)	40 (52%)	1.000
Venlafaxine	20 (48%)	38 (48%)		21 (49%)	37 (48%)	
Age (years)						
Mean (SD)	40.1 (10.8)	40.2 (11.8)	0.877	40.0 (12.1)	40.4 (11.1)	0.871
18–29	10 (24%)	19 (24%)	0.959	10 (22%)	19 (25%)	0.911
30–44	17 (40%)	30 (38%)		19 (42%)	28 (36%)	
45–59	14 (33%)	29 (37%)		15 (33%)	29 (38%)	
≥ 60	1 (2%)	1 (1%)		1 (2%)	1 (1%)	
Sex						
Female	16 (38%)	17 (22%)	0.057	10 (22%)	23 (30%)	0.404
Male	26 (62%)	62 (78%)		35 (78%)	54 (70%)	
Race/ethnicity						
Non-Hispanic White	23 (55%)	47 (59%)	0.161	22 (49%)	49 (64%)	0.129
Hispanic or Latino	1 (2%)	9 (11%)		4 (9%)	6 (8%)	
Non-Hispanic Black	16 (38%)	22 (28%)		19 (42%)	19 (25%)	
Asian/Pac.Islander	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Other	2 (5%)	1 (1%)		0 (0%)	3 (4%)	
Education						
< HS	8 (20%)	11 (15%)	0.601	10 (23%)	9 (12%)	0.195
≥ High School	33 (80%)	64 (85%)		34 (77%)	64 (88%)	
Years Since Injury						
Mean (SD)	11.6 (9.6)	11.2 (11.3)	0.574	12.5 (11.6)	10.8 (10.3)	0.638
≤ 1 year	2 (5%)	6 (8%)	0.712	4 (9%)	4 (5%)	0.465
> 1 year	40 (95%)	73 (92%)		41 (91%)	73 (95%)	
AIS						
A	23 (55%)	44 (56%)	0.951	25 (56%)	42 (55%)	0.946
B	5 (12%)	12 (15%)		7 (16%)	11 (14%)	
C	4 (10%)	7 (9%)		3 (7%)	8 (10%)	
D	10 (24%)	16 (20%)		10 (22%)	16 (21%)	
Severity of SCI						
Tetraplegia, complete	9 (21%)	14 (18%)	0.745	9 (20%)	14 (18%)	0.700
Tetraplegia, incomplete	13 (31%)	19 (24%)		10 (23%)	23 (30%)	
Paraplegia, complete	14 (33%)	29 (37%)		15 (34%)	28 (36%)	
Paraplegia, incomplete	6 (14%)	16 (21%)		10 (23%)	12 (16%)	
Cause of Injury						
Fall	4 (10%)	13 (16%)	0.752	3 (7%)	14 (18%)	**0.048**
Vehicular	16 (38%)	27 (34%)		12 (27%)	31 (40%)	
Gunshot	13 (31%)	26 (33%)		20 (44%)	19 (25%)	
Other Violence	0 (0%)	1 (1%)		0 (0%)	1 (1%)	
Other	9 (21%)	12 (15%)		10 (22%)	12 (16%)	
Marital Status						
Never Married	25 (60%)	40 (51%)	0.744	27 (60%)	39 (51%)	0.694
Married	12 (29%)	27 (35%)		13 (29%)	26 (34%)	
Div/Sep/Wid	5 (12%)	11 (14%)		5 (11%)	11 (14%)	
Employed						
No (>1)	33 (80%)	65 (83%)	0.801	37 (84%)	62 (82%)	0.807
Yes (1)	8 (20%)	13 (17%)		7 (16%)	14 (18%)	
Baseline Drug Use						
Tobacco products	18 (46%)	33 (49%)	0.841	16 (41%)	35 (51%)	0.321
Any non-tobacco	19 (49%)	48 (72%)	**0.023**	26 (67%)	42 (62%)	0.679
Cannabis	8 (21%)	26 (39%)	0.056	14 (36%)	21 (31%)	0.670
Cocaine	2 (5%)	3 (4%)	1.000	3 (8%)	3 (4%)	0.666
Stimulants	0 (0%)	1 (1%)	1.000	1 (3%)	0 (0%)	0.365
Inhalants	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	—

Continued

Table 1 *Continued*

Variable	Any NP Pain		P	Any NC Pain		P
	No	Yes		No	Yes	
	N = 42	N = 79		N = 45	N = 77	
Sedative/hypnotics	14 (36%)	25 (37%)	1.000	18 (46%)	22 (32%)	0.213
Hallucinogens	0 (0%)	0 (0%)	—	0 (0%)	0 (0%)	—
Opioids	14 (36%)	33 (49%)	0.225	16 (41%)	32 (47%)	0.687
Depression (PHQ-9; baseline)						
Mean (SD)	14.4 (3.1)	15.6 (3.9)	0.143	16.0 (4.2)	14.8 (3.3)	0.115
PHQ < 10	1 (2%)	1 (1%)	1.000	1 (2%)	1 (1%)	1.000
PHQ ≥ 10	40 (98%)	78 (99%)		44 (98%)	75 (99%)	
Current Anxiety						
Mean (SD)	9.7 (4.7)	12.1 (5.5)	0.026	12.4 (5.4)	10.5 (5.2)	0.075

Significance by Fisher Exact and Mann-Whitney as appropriate. NP = Neuropathic pain; NC = nociceptive pain; UW = University of Washington; UAB = University of Alabama at Birmingham; UM = University of Michigan; RIC = Rehabilitation Institute of Chicago; BIR = Baylor Institute for Rehabilitation; Miami = University of Miami; HS = high school; AIS = American Spinal Injury Association Impairment Scale.

characteristics of both the NP and NC samples, including mean depression and anxiety levels, see Table 1.

Table 2 shows descriptive statistics for pain and outcome measures. Of those reporting pain, many had, on average, more than one pain type. Approximately 74% had pain that was classified as neuropathic, and 70% had pain that was classified as non-neuropathic or nociceptive, indicating the presence of both pain types in most participants. The average reduction in pain severity and pain interference for each pain type was similar, with the exception of a slightly larger reduction in neuropathic pain interference. According to Diener's interpretation of SWLS score ranges,[37] baseline SWLS scores for those with both NP and NC pain types indicated these individuals to be generally dissatisfied or to have substantial dissatisfaction with their lives. Follow-up scores increased, on average, to a range that is considered slightly below average in life satisfaction.

Table 2 Means and standard deviations for baseline and follow-up pain severity, pain interference and QoL outcome measures

	NP Pain	NC Pain
Subjects Reporting Pain	90	86
Pain sites per subject	1.7 (0.7)	1.7 (0.7)
Subjects with both pain types	54 (60%)	54 (63%)
Baseline		
Average Pain Intensity*	3.8 (2.1)	3.4 (1.9)
Average Pain Interference*	3.2 (2.2)	2.4 (1.6)
SWLS	12.2 (5.4)	12.3 (5.2)
SF-12 Physical	32.7 (12.3)	34.5 (13.2)
SF-12 Mental	31.3 (10.3)	31.4 (9.6)
Outcome (12 weeks)		
Subjects Followed	79 (88%)	77 (90%)
Mean change in Pain Intensity*	–0.9 (1.4)	–0.9 (1.7)
Mean change in Pain Interference*	–1.2 (1.5)	–0.9 (1.3)
Mean change in SWLS	4.3 (6.0)	4.4 (6.7)
Mean change in SF-12p	5.1 (12.3)	5.2 (13.8)
Mean Improvement in SF-12m	14.7 (16.4)	14.1 (17.3)

* Based on the three-site average calculated for each individual. Since some individuals had both pain types, the sample sizes for both groups do not total the overall sample reporting any pain at (N = 122) or those with pain outcomes at follow-up (N = 108).

Neuropathic pain

Results of the regression models examining the relationship between neuropathic pain severity and interference on QoL outcomes and the CHART Mobility and Physical Independence scores are shown in Tables 3 and 4, respectively. When modeling the relationship between change in neuropathic pain severity and SWLS at 12-week follow-up, only treatment group emerged as a significant predictor, with no association with neuropathic pain severity. Treatment group and being of non-white ethnicity were also associated with higher follow-up SF12 MCS scores, but neuropathic pain severity was not. There was similarly no relationship between change in neuropathic pain severity and SF12 PCS scores or the CHART measures. When using neuropathic pain interference as a predictor of QoL and accounting for baseline QOL, being of non-white ethnicity predicted improvements in SF12-MCS scores. Less neuropathic pain interference at baseline, but not neuropathic pain interference at follow-up, was significantly associated with better SF12p outcomes. Neuropathic pain interference across the 12 weeks was not related to CHART Physical Independence or Mobility scores at follow-up (Table 4).

Nociceptive pain

Results of the regression models examining the relationship between nociceptive pain severity and interference on QoL outcomes and the CHART Mobility and Physical Independence scores are shown in Tables 3

Table 3 Results of linear regression models predicting QoL outcomes by pain subtype, including the retained covariates of treatment arm and race

		NP (N = 79)			NC (N = 77)		
QOL Outcome	Model Effect	B	SE	P	B	SE	P
SWLS	Venlafaxine	2.91	1.37	**0.037**	1.03	1.56	0.514
	White	–3.00	1.67	0.077	–3.67	1.84	**0.050**
	SWLS (Baseline)	0.80	0.13	0.000	0.87	0.14	0.000
	Sites	0.92	1.74	0.598	–0.28	1.53	0.856
	Pain Score (12 week)	–0.32	0.73	0.666	0.38	0.67	0.573
	Pain Score (Baseline)	–0.18	0.56	0.749	–0.90	0.55	0.106
	Venlafaxine	2.65	1.40	0.062	0.39	1.53	0.799
	White	–2.53	1.65	0.129	–3.82	1.72	**0.030**
	SWLS (Baseline)	0.77	0.14	0.000	0.81	0.13	0.000
	Sites	0.19	1.46	0.896	0.48	1.28	0.710
	Interference (12 week)	0.13	0.66	0.849	0.12	0.71	0.869
	Interference (Baseline)	–0.48	0.59	0.415	–1.47	0.64	**0.024**
SF12 PCS	Venlafaxine	–1.36	2.61	0.603	–5.57	3.34	0.100
	White	5.71	3.20	0.079	8.04	3.95	**0.046**
	SF12p (Baseline)	0.59	0.13	0.000	0.42	0.13	0.002
	Sites	–3.98	3.37	0.243	–2.26	3.12	0.471
	Pain Score (12 week)	1.25	1.44	0.388	1.66	1.36	0.228
	Pain Score (Baseline)	–1.38	1.06	0.197	–1.27	1.12	0.262
	Venlafaxine	–2.12	2.57	0.413	–5.94	3.43	0.088
	White	5.50	3.04	0.075	7.13	3.73	0.061
	SF12p Baseline	0.51	0.13	0.000	0.40	0.16	0.015
	Sites	–1.50	2.66	0.573	0.47	3.05	0.879
	Interference (12 week)	0.25	1.28	0.845	0.62	1.60	0.701
	Interference (Baseline)	–2.19	1.05	**0.041**	–1.91	1.35	0.163
SF12 MCS	Venlafaxine	6.67	3.16	**0.038**	5.60	4.13	0.180
	White	–14.77	3.88	**0.000**	–11.52	5.02	**0.025**
	SF12 m Baseline	0.49	0.16	0.004	0.30	0.20	0.144
	Sites	1.68	3.99	0.675	–3.56	3.84	0.358
	Pain Score (12 week)	0.02	1.67	0.991	0.97	1.74	0.577
	Pain Score (Baseline)	–0.97	1.28	0.451	–1.40	1.41	0.322
	Venlafaxine	5.72	3.17	0.075	3.24	4.08	0.430
	White	–13.80	3.75	**0.000**	–11.67	4.61	**0.014**
	SF12 m Baseline	0.48	0.16	0.005	0.28	0.20	0.150
	Sites	1.05	3.26	0.748	–2.62	3.22	0.419
	Interference (12 week)	0.71	1.49	0.634	1.41	1.82	0.441
	Interference (Baseline)	–2.02	1.30	0.126	–3.61	1.66	**0.033**

SWLS = Satisfaction with life; SF12 PCS = Short Form 12 Health Survey physical component score; SF12 MCS = Short Form 12 Health Survey mental component survey.

and 4, respectively. Race/ethnicity (non-white) predicted higher SWLS, SF12 PCS and SF12 MCS follow-up scores. Lower baseline nociceptive pain interference, but not nociceptive pain interference at follow-up, was associated with better SWLS and SF12 MCS outcome scores. Nociceptive pain severity or interference across time was not related to SF-12 PCS or the CHART Mobility or Physical Independent outcome scores.

Discussion

The primary purpose of this study was to examine the relationship between pain severity and interference on QoL outcomes in persons with SCI, and whether the relationship differed by type of SCI-related pain. Results revealed that baseline nociceptive pain interference, but not nociceptive interference at 12-week follow-up, was significantly and inversely associated with higher satisfaction with life and mental components of QOL when accounting for race/ethnicity and whether participants had received venlafaxine. Similarly, lower neuropathic pain interference at baseline, but not at 12-week follow-up, was significantly associated with better physical components of QOL outcomes. Neuropathic or nociceptive pain severity measured across the 12 weeks were not related to any of the QoL outcomes. Broadly, this suggests that nociceptive and neuropathic pain types, at least with respect to the interference associated with each in life activities, may potentially have differential relationships to QoL outcomes following SCI. Further, the relationship between nociceptive pain interference and subsequent QOL may be fairly stable in persons with depression despite treatment with venlafaxine.

Table 4 Results of linear regression models predicting CHART outcomes from changes in pain subtype, including the retained covariates of treatment arm and race

CHART Outcome	Model Effect	NP (N = 79)			NC (N = 77)		
		B	SE	P	B	SE	P
Mobility	Venlafaxine	3.33	3.30	0.317	2.27	3.61	0.531
	White	3.93	4.11	0.342	0.57	4.72	0.904
	Mobility Baseline	0.63	0.08	0.000	0.73	0.08	0.000
	Sites	4.33	4.11	0.296	2.66	3.33	0.426
	Pain Score (12 month)	0.11	1.74	0.950	–2.68	1.52	0.082
	Pain Score (Baseline)	–1.46	1.33	0.275	–1.54	1.23	0.214
	Venlafaxine	3.12	3.40	0.362	1.33	3.86	0.731
	White	4.24	4.06	0.301	1.58	4.80	0.744
	Mobility Baseline	0.62	0.08	0.000	0.74	0.08	0.000
	Sites	3.71	3.39	0.278	–1.71	3.02	0.573
	Interference (12 month)	–0.41	1.59	0.799	–0.54	1.71	0.755
	Interference (Baseline)	–0.63	1.37	0.650	–2.08	1.55	0.185
Physical Independence	Venlafaxine	–3.29	6.39	0.608	–0.95	7.66	0.901
	White	2.23	8.16	0.786	2.61	10.09	0.797
	PI Baseline	0.66	0.10	0.000	0.79	0.10	0.000
	Sites	12.45	8.13	0.131	–3.46	6.87	0.616
	Pain Score (12 month)	–2.72	3.42	0.429	1.68	3.16	0.597
	Pain Score (Baseline)	3.26	2.56	0.207	–1.22	2.58	0.639
	Venlafaxine	–1.74	6.50	0.790	1.16	7.74	0.881
	White	1.00	8.05	0.902	–1.09	9.56	0.910
	PI Baseline	0.66	0.10	0.000	0.81	0.10	0.000
	Sites	13.12	6.66	0.053	–1.21	5.97	0.840
	Interference (12 month)	–2.91	3.02	0.339	–0.59	3.38	0.861
	Interference (Baseline)	3.77	2.63	0.156	0.66	3.14	0.833

PI Baseline = Baseline CHART Physical Independence scores.

Pain following SCI is not a unitary phenomenon, with nociceptive and neuropathic types associated with different symptom profiles, pathophysiology and treatment. Yet most of the research to date on the effects of SCI-related pain on QoL have examined pain generally, without distinguishing between type.[10,12–19,21] The few studies that distinguish between pain types have done so on somewhat of a de facto basis, for example, examining shoulder pain in manual wheelchair users[45,46] and therefore studying what was likely an above-level, nociceptive pain. In those studies, significant relationships were found between QoL and degree of nociceptive pain. One longitudinal trial[45] similarly found that changes in nociceptive pain across 12 weeks were related to improvement in subjective quality of life. However, results from this present study did not find any relationship between nociceptive pain severity on psychosocial aspects of QoL as measured by the SWLS. While venlafaxine XR improved nociceptive pain[27] and also QOL[26] in the larger trial, it does not appear that there is any direct relationship between nociceptive pain severity and QOL across time. QoL is often measured globally, with many different measures used to quantify this construct. The fact that no relationship was found between nociceptive pain severity and QOL compared to prior studies suggests that distinct domains of QoL, represented by different questionnaires or measures, may exist and may be differentially sensitive to improvement in or worsening of nociceptive pain following SCI.

A reasonable assumption is that decreasing nociceptive pain severity and in particular, nociceptive pain interference, would be associated with improved physical independence or mobility across time, yet we did not find such an association. In a longitudinal trial of shoulder pain in SCI, Kemp and colleagues[45] did find that reducing that pain was associated with increased participation in social activities, but physical independence and mobility per se were not specifically measured. In one cross-sectional study on men with SCI that used the same CHART subscales,[47] mobility and physical independence were not related to pain severity; however, location of the pain was associated with mobility. Individuals with upper extremity pain were more likely to have lower mobility scores than those who had pain elsewhere, although it is unclear if the upper extremity pain represented neuropathic or nociceptive pain. At least with respect to neuropathic pain, location of pain relative to injury is believed to reflect different underlying pathophysiology and symptom manifestation,[48] suggesting that a dichotomous distinction of being either present or absent is not sufficient for characterizing the two pain types examined in this study. While this study addressed one

gap in the literature—how pain severity and interference affects QoL, mobility and interference *across time*—accounting for location of the pain and specific sensory profiles (e.g. continuous or episodic, presence of allodynia or hyperalgesia) may reveal different effects on these outcomes.

When neuropathic pain specifically was examined, we found only a marginal effect of the degree of interference from neuropathic pain at baseline and improved better physical health-related QOL outcomes. No relationships whatsoever emerged with neuropathic pain severity across time and any aspect of QoL, physical independence and mobility outcomes. This is in contrast to a review by Jensen *et al*[49] who found that the presence and severity of neuropathic pain was associated with greater impairments across a number of health-related QoL domains. Their review, however, included studies using populations with varying etiologies of neuropathic pain (peripherally vs. centrally mediated), were often cross-sectional, and were not specific to SCI. The results from the present study suggest that at least across time, other factors may explain QoL, above and beyond the severity and degree of interference that neuropathic pain may cause.

There are several limitations to note. All participants had comorbid major depressive disorder, and therefore the current results may not be generalizable to those with SCI and pain who are not depressed. Additionally, the SCIPI is a subjective measure of neuropathic pain versus non-neuropathic/nociceptive pain; nevertheless, the overall accuracy of the SCIPI (76%) is not that different from how well expert raters come to consensus on the distinction.[41] Higher doses of venlafaxine, compared to the lower doses used to treat depression in this study, are typically needed to produce the noradrenergic effects believed to be helpful for neuropathic pain.[50] This suggests that there may have been insufficient change in neuropathic pain as a result of the study design to detect relationships with QoL outcomes.

Lastly, this study was likely somewhat underpowered to adequately detect the relationships of interest in these analyses. Moreover, with no alpha inflation correction for multiple statistical tests, caution is warranted when interpreting the few relationships that emerged based on a standard critical P-value. A major challenge in SCI-pain clinical trials is that pain types are not mutually exclusive, even when modeling one type of pain and controlling for the number of pain sites experienced by an individual, as was done in this study. There are potential interactive or moderating effects within the individual who has both types of SCI-related pain. A person with SCI who has both neuropathic and nociceptive pain may experience improvement in one type but not the other, and therefore still experience limitations in mobility and physical independence or certain facets of QoL, for that matter. Design and implementation of future trials examining SCI-related pain should consider the complex nature of pain that occurs following SCI and follow appropriate methods for sufficiently powering trials examining specific pain outcomes.[24]

Conclusions

Nociceptive and neuropathic types of SCI-pain severity do not appear related to QoL outcomes following SCI, at least when measured across a 12-week timeframe. Baseline pain interference was differentially associated with QoL outcomes depending on the type of SCI-pain. Broadly, however, there was no evidence to implicate extensive relationships between pain and QoL generally in this sample of depressed persons with SCI. Given that the relationship between pain is extensive in the literature, future studies should re-examine potential differences in QoL outcomes and possible complex relationships with mobility and independence based on pain type with a larger, non-depressed sample. If a clinical trial for SCI-related pain is of interest, treatment doses consistent with purported analgesic effects for neuropathic pain should be used.

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